What we need from the mathematics teacher is, not for them to produce young men who can juggle equations, but to produce young men who can recognize the relations of things.

My limit of time is presumably exhausted, and I will conclude. You probably will not all now agree with my opinions, but fair opinions honestly spoken ought to offend no one; and I am satisfied that my opinions will be sustained in the minds of the majority of experienced teachers in engineering colleges who have given careful thought to the question before us. When the University of Wisconsin puts into effect a year hence its promulgated additional requirements in algebra preparation for students entering the college of engineering, it is not so much because we particularly care for more pages of the book to be covered in the high schools, but because we hope that the students (with more time allotted to the subject) may attain more of the true powers of reasoning that come from searching for and recognizing the relations of things.

If a teacher's pupils are capable of transforming (juggling) equations correctly according to rule, without giving a thought to the meaning of the forms produced, or are capable of following through an arithmetical problem by the approved method without considering the reasonable accuracy of the numerical results, then that teacher's sowing has been choked with tares. But a teacher of mathematics who leads his pupils to give due thought in the course of their work to interpreting equations, to noticing the relations of things, and to scrutinizing and checking the accuracy of every numerical result (even though the pupils may evolve, for their own use, awkward and unapproved analytical methods)—that teacher's sowing is of golden wheat.

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THEORIES OF METABOLISM.[1]

The sum of the chemical changes which take place within the organism under the influence of living cells is called metabolism. This paper is to discuss the character of these changes and to consider, as far as we may, their cause.

It was Lavoisier who first understood that oxygen supported combustion and he compared life with the flame of a candle. He conceived the idea that hydrogen and carbon were brought to the lungs by the blood and there united with oxygen. It was, however, observed that the heat production was not confined to the lungs, and when Magnus found that venous blood was richer in carbon dioxide and poorer in oxygen than was arterial blood, the process of oxidation was placed in the blood. Ludwig in his later years believed this. The prevailing view, however, is that the processes of metabolism take place within the cells of the body.

Lavoisier believed that oxygen was the cause of the metabolism. Liebig thought that fat and carbohydrates were destroyed by oxygen, while proteid metabolism took place on account of muscle work. Voit showed that muscle work did not increase proteid metabolism and that the metabolism was not proportional to the oxygen supply. The amount of oxygen absorbed apparently depended upon what metabolized in the cells. He showed that although fat burned readily in the air, it burned only with great difficulty in the body; and that proteid burned with comparative difficulty in the air, but went to pieces very readily in the body. Voit believed that the cause

[1] A paper read before the New York Section of the American Chemical Society.

of metabolism was unknown, but that the process was one of cleavage of the food molecules into simpler products which could then unite with oxygen. Yeast cells, for example, convert sugar into carbon dioxide and alcohol without the intervention of oxygen. In like manner the first products of the decomposition of fat, sugar and proteid are formed in metabolism through unknown causes. Some of these preliminary decomposition substances may unite with oxygen to form carbon dioxide and water, others may be converted into urea, while others under given circumstances may be synthesized to higher compounds. In any case the absorption of oxygen does not cause metabolism, but rather the amount of the metabolism determines the amount of oxygen to be absorbed.

The statement is frequently met with in the literature of the subject that such and such a disease is the consequence of deficient oxidation power in the tissues. For example, it has recently been stated that alcohol decreases the oxidation power of the liver for uric acid. Such apparent decrease in oxidation power may be due to the fact that the protoplasm is so altered that the normal oxidizable cleavage products of uric acid are not formed and, therefore, no oxidation can take place. It is not due to lack of oxygen that sugar does not burn in diabetes, or cystin in cystinuria. There is the normal supply of oxygen present, but the cleavage of these substances into bodies which can unite with oxygen can not be effected, and hence they can not burn.

There is a difference of opinion as to whether the food substances must first become vital integers of the living cell, or whether the non-living food materials are metabolized without ever becoming a constituent part of the living protoplasm.

Pflüger holds the former view that incorporation of nutritive matter with the living substance is essential to its metabolism. He conceives that living proteid may contain the labile cyanogen group in contrast with dead proteid which contains the amino group. He illustrates this by Wöhler's classic experiment of the easy conversion of ammonium cyanate into urea.

$$NH_4OCN = (NH_2)_2CO$$

Voit's theory is that the living proteid is comparatively stable and that food proteid which becomes the circulating proteid of the blood is carried to the cells and promptly metabolized. The other foodstuffs are also burned without first entering into the composition of the cell.

A mass of living cells composing the substance of a warm-blooded animal has the same requirement of energy as any similar mass of living cells composing the substance of any other animal of the same size and shape. The reason for the metabolism lies in unknown causes within the cells. Liebig conceived the cause to be due to the swinging motion of the small constituent particles of the cells themselves. If this hypothesis be accepted the vibrations of the cells may be assumed to shatter the proteïd molecule into fragments consisting of amino bodies, and to break down fat and sugar into substances of a lower order than themselves.

The uniformity of the energy requirement is illustrated by the following table showing the number of calories given off during the twenty-four hours by one square meter of surface in various animals and in man, in the condition of starvation.

	Weight in kilos.	Cal per sq. m. Surface.
Man	64	1042
Pig	128	1078
Dog	15	1039
Mouse	0.018	1188
Diabetic man	54	925

This illustrates Rubner's law of skin area, which holds that the metabolism is

proportional to the exposed area of the animal.

Even in pathological conditions a remarkable constancy of total heat production is apparent. Thus in such typical disturbances as anæmia, diabetes, gout and obesity, the general laws governing the output of carbon dioxide, the absorption of oxygen and the production of heat are found to be the same as in health. In fever the metabolism and heat production increase and this to a certain extent on account of the warming of the cells. In exophthalmic goiter there is probably an increase in metabolism, due to the chemical stimulus of an excessive production of iodothyrin in the thyroid gland, while in myxœdema the absence of the same substance causes a considerable reduction in the metabolism. Drugs may influence the course of the metabolism, iodothyrin increasing it and morphine profoundly diminishing it, but on the whole the most striking fact is not the variability, but rather the uniformity, of the processes concerned.

Within recent years the work of Kossel, Fischer, Hofmeister and Levene has given a more definite conception of the composition of proteid than was before possible. There is every indication that the proteid molecule consists fundamentally of groups of amino fatty acids banded together. Proteids vary with the integral components of their chemical chains. It has long been known that the end products of tryptic digestion include such substances, but Kutscher first showed that continued tryptic digestion resulted in the complete transformation of proteid into these amino-acids. Cohnheim discovered erepsin, an enzyme derived from the intestinal wall, which rapidly converts albumoses into these substances.

On chemical analysis, using methods developed in Emil Fischer's laboratory, the cleavage products of various proteids appear distributed as shown in the following table.[2]

COMPOSITION OF PROTEID.

	Casein.	Gelatin.	Elastin.	Globin from Hæmaglobin.	Edestin.
Glycocoll	0	16.5	25.75	0	3.8
Alanin	0.9	0.8	0.58	4.19	3.6
Leucin	10.5	2.1	21.38	29.04	20.9
Pyrrolidin carboxylic acid	3.1	5.1	1.74	2.34	1.7
Phenylalanin	3.2	0.4	3.89	4.24	2.4
Glutamic acid	10.7	0.88	0.76	1.73	6.3
Aspartic acid	1.2	0.56	—	4.43	4.5
Cystin	0.065	—	1.0	0.31	0.25
Serin	0.23	—	—	0.56	0.33
Oxy-γ-Pyrrolidin carboxylic acid	0.25	3.0	—	1.04	2.0
Tyrosin	4.5	—	0.34	1.33	2.13
Anninovalerianic acid	1.0	—	—	—	*
Lysin	5.80	2.75	—	4.28	2.0
Histidin	2.59	7.62	—	10.90	1.0
Arginin	4.84	0.40	0.3	5.42	11.7
Tryptophan	1.5	—	—	*	*

* Present.

The proteid metabolism in plants and animals occurs in striking similarity to the changes brought about by enzymes and hydrolytic agents acting on proteid outside of the tissues. Thus in the germinating seed Schultze[3] finds that asparagin, leucin, tyrosin, histidin, arginin and lysin arise from the metabolism of proteid. The occurrence of leucin and tyrosin in the liver and urine in such diseased conditions as phosphorus poisoning has long been known and Abderhalden and Bergell[4] report the presence of glycocoll in rabbit's urine after the administration of phosphorus. Urine after phosphorus poisoning may also contain phenylalanin[5] and arginin.[6] Wakeman[7] finds an altered quan-

[2] Abderhalden, E., *Zeitschr. f. physiol. Chem.*, 1905, Bd. 44, p. 17.

[3] Schultze and Castero, *Zeitschrift für physiologische Chem.*, 1904, Bd. 44, p. 455.

[4] Abderhalden and Bergell, *Zeitschrift für physiologische Chem.*, 1903, Bd. 39, p. 464.

[5] Abderhalden and L. F. Barker, *Zeitschrift für physiologische Chem.*, 1904, Bd. 42, p. 524.

[6] Wohlgemuth, *Zeitschrift für physiologische Chem.*, 1905, Bd. 44, p. 74.

[7] Kossel, *Berliner klinische Wochenschrift*, 1904. No. 41.

titative relationship between histidin, arginin and lysin in the composition of liver substance after phosphorus poisoning, arginin in particular, being reduced below the quantity found in the liver of the normal dog. This possibly suggests a specific action by phosphorus on certain cell proteids rich in arginin which are essential to vitality. All forms of proteid decomposition follow, therefore, the pathway of cleavage into amino acids.

The question arises, to what extent may the amino bodies formed within the intestine be regenerated into proteid? It is believed that the cells of the intestinal villus regenerate fat from fatty acid and glycerin, since neutral fat alone is found in the thoracic duct. But all the starch fed is not regenerated into starch, nor is maltose regenerated into maltose in the body. Much may be burned as dextrose and only a part is transformed into glycogen. Long ago Schultzen and Nencki[8] stated that a certain amount of amino bodies formed in digestive proteolysis was absorbed and burned, and that the absorbed proteid itself followed the lines of an enzymatic cleavage into amino bodies. In the light of newer knowledge several authorities have recently elaborated theories along similar lines. It has been pointed out by Folin[9] that there is little evidence of reconstruction of all the proteid ingested. He cites the experiments of Nencki and Zaleski,[10] which showed that the portal blood during digestion contains four times as much ammonia as arterial blood, and that the mucosa of both stomach and intestine yield large quantities of ammonia. The inference is that the ammonia of the portal vein is derived from ammonia produced in the mucosa as well as from that which normally originates in the intestine during tryptic proteolysis.

[8] Schultzen and Nencki, *Zeitschrift für Biologie*, 1872, Bd. 8, p. 124.

[9] Folin, *American Journal of Physiology*, 1905, Vol. 13, p. 117.

[10] Nencki and Zaleski, *Zeitschrift für physiologische Chem.*, 1901, Bd. 33, p. 206.

The existence of denitrogenizing enzymes is afforded by the example of the guanase and adenase of Walter Jones,[11] which respectively convert guanin into xanthin and adenin into hypoxanthin with the liberation of ammonia.

Folin believes that the greater part of the proteid ingested undergoes a denitrogenization through the hydrolysis of the amino cleavage products. Such a reaction would read

$$\equiv CNH_2 + H_2O = \quad COH + NH_3.$$

The ammonia may be converted into urea within the organism, and the nitrogen free rest may be converted into sugar. The simplest expression of this is seen in the experiment of Neuberg and Langstein,[12] who found glycogen in the liver and lactic acid in the urine of a rabbit following the ingestion of alanin. The transformation of alanin into lactic acid may be written

$$\underset{\text{Alanin.}}{CH_3\cdot CHNH_2\cdot COOH} + H_2O = \underset{\text{Lactic Acid.}}{CH_3\cdot CHOH\cdot COOH} + NH_3.$$

The transformation of lactic acid into sugar is demonstrated by the experiment of A. R. Mandel,[13] who showed an increase in the sugar output in diabetes after the ingestion of lactic acid.

Stiles and Lusk[14] have shown that ingestion of the mixture of amino bodies produced from the tryptic digestion of meat may yield sugar in large quantity in diabetes.

[11] Jones and Winternitz, *Zeitschrift für physiologische Chemie*, 1905, Bd. 44, p. 1.

[12] Neuberg and Langstein, *Archiv für Physiologie*, Suppl. Bd., 1903, p. 514.

[13] Mandel, 'Proceedings of the American Physiological Society,' *Am. Jour. of Physiol.*, 1905, Vol. 13, p. xvi.

[14] Stiles and Lusk, *American Journal of Physiology*, 1903, Vol. 9, p. 380.

Wolf[15] finds that none of these amino substances has any effect on the blood pressure of animals, so far as he has examined them.

Although some proteid metabolism may take place as above outlined, it is an undoubted fact that proteid may be synthesized in the body with the formation of new tissue, and also that proteids injected into the blood stream, as in cases of transfusion of blood serum, are rapidly destroyed and the nitrogen eliminated as urea. The conditions of proteid metabolism may, therefore, be entirely similar to those of starch metabolism, (1) digestive hydrolysis, (2) partial combustion of the end products, and (3) possible regeneration of portions of the end products into substances similar to the originals, but characteristic of the organism, *i. e.*, glycogen and body proteids. In the case of proteids the second or metabolic process involves the partial passage of the end products through the glucose stage. The third or regenerative process is promoted by such a proteid as casein, which yields a variety of cleavage products.

Folin[16] has discovered that a man fed with creatin free food eliminates a constant quantity of creatinin nitrogen in the urine irrespective of the amount of nitrogen ingested with the food. Thus the urine of one man contained 16.8 grams of total nitrogen with 0.58 gram of creatinin nitrogen. The same man at another time, after large carbohydrate ingestion, eliminated 3.60 grams of total nitrogen and 0.60 gram of creatinin nitrogen. Folin conceives that the constancy of the creatinin and uric acid output is a true index to the necessary protoplasmic breakdown, and would define the nitrogen of such destruction as the endogenous nitrogen. To what extent, if any, urea nitrogen enters into this essential life metabolism he is not prepared to say. The same idea was expressed by Burian[17] in an article published ten days later than Folin's. Burian believes that purin bases are a constant product of muscle metabolism and that these are oxidized to uric acid, a part of which is further converted into urea. This process of itself would evolve urea as a constant product of the endogenous nitrogen metabolism. According to this newer conception the cells of the body through the swinging motion of their particles do continually break down their own protoplasm with the production of creatinin, purin bases, and perhaps other substances. These same cells may also break up exogenous amino radicles derived from ingested proteid or circulating proteid itself.

Neuberg and Loewi[18] have made an observation which is not in accord with the idea that proteid metabolism normally passes through the amino-acid stage. These authors investigated a case of cystinuria, a condition in which cystin formed from proteid can not be burned, but is eliminated in the urine. After ingesting leucin, tyrosin and aspartic acid these also were almost quantitatively eliminated in the patient's urine, although the normal organism burns them. Since these substances were not eliminated by the patient on a normal diet, the presumption is that they can not be normal products of intermediary proteid metabolism. The authors find it difficult to explain this according to the conception of a general breakdown of proteid into amino acids. This experiment lacks confirmation.

[15] Wolf, *Journal of Physiology*, 1905, Vol. 32, p. 171.

[16] Folin, *American Journal of Physiology*, 1905, Vol. 13, p. 66.

[17] Burian, *Zeitschrift für physiologische Chem.*, 1905, Bd. 43, p. 532.

[18] Neuberg and Loewi, *Zeitschrift für physiologische Chemie*, 1904, Bd. 43, p. 338.

As regards fat metabolism Geelmuyden[19] is inclined to the opinion that oxybutyric acid, aceto-acetic acid and acetóne are normal metabolism products derived from members higher up in the series.

As regards dextrose Stoklasa[20] announces that all animal and vegetable cells contain enzymes capable of converting dextrose into alcohol and carbon dioxide. He[21] also finds a ferment in animal tissues able to convert sugar into lactic acid. He quotes Oppenheimer's experiment, showing that whereas fresh normal blood yielded little lactic acid on standing at 37° C., much greater amounts were formed if dextrose was added. He believes that this lactic acid is subsequently converted into alcohol and carbon dioxide.

Embden[22] comes to the conclusion that blood sugar perfused through the liver may be broken up into lactic acid. It has been previously shown that lactic acid could be converted into dextrose and it is a curious fact that this same dextrose may pass through the lactic-acid stage on its way to oxidation.

A. R. Mandel[23] in the writer's laboratory has shown that lactic acid disappears from the blood and urine in phosphorus poisoning if diabetes be induced. Here the mother substance of the accumulating lactic acid is removed in the urine. Any considerable production of alcohol in tissue metabolism, while possible, does not seem probable in light of the known physiological action of the substance.

[19] Geelmuyden, *Zeitschrift für physiologische Chem.*, 1904, Bd. 41, p. 128.

[20] Stoklasa, *Centralblatt für Physiologie*, 1903, Bd. 17, p. 465.

[21] Stoklasa, Jelinck und Cerny, *Centralblatt für Physiologie*, 1903, Bd. 16, p. 712.

[22] Embden, 'Verhandlungen der 6sten Internationalen physiologen Congress,' *Centralblatt für Physiologie*, 1905, Bd. 18, p. 832.

[23] Mandel, 'Proceedings of the Am. Physiol. Society,' *American Journal of Physiology*, 1905, Vol. 13, p. xvi.

Rubner[24] gives the following theory of metabolism: Living proteid, through the vibrations of its particles, metabolizes the food substances. The action resembles catalysis. The energy liberated reacts on the particles of protoplasm, causing a change in their position and a cessation of metabolism. The particles then return to their original position and the cycle begins again. These processes require a fixed amount of energy. Rubner does not give his reasons for believing in this rhythm of excitation and rest.

The quantity of the combustion depends on the power of the cells to metabolize (Voit). In the resting state this metabolic power of the cells is influenced by the 'law of skin area' (Rubner). Temperature (cooling or warming) and nerve excitation (muscle work, chemical regulation) affect the power of the cells to metabolize, perhaps through an increase in the oscillation of the particles, an effect which is in turn maintained at the expense of the energy derived from metabolism. Living protoplasm metabolizes in accord with its necessities at the time, and never more. Large quantities of nutrient materials furnished will not increase cell metabolism. If food be ingested above the requirement for the organism, any excess will be retained in the body. The kind of metabolism depends upon the constitution of the fluid feeding the cells, and whether proteid, carbohydrates or fats have been ingested.

Each ingested foodstuff exerts a specific dynamic action (Rubner). At a temperature of 33° C. the ingestion of the starvation requirement of energy in the form of fat increases the requirement for energy ten per cent., carbohydrates raises it five per cent., proteids thirty per cent. In other words, in the case of meat, in order to obtain calorific equilibrium about 140 calories

[24] Rubner, 'Von Leyden's Handbuch der Ernährungstherapic,' 1903, p. 78.

must be ingested instead of 100, if that represents the starvation requirement. Rubner[25] explains that the cells of the body do not require more energy after meat ingestion than in starvation, but that the heat produced by a preliminary cleavage of proteid into dextrose on the one hand, and into a nitrogen containing rest on the other, while yielding heat to the body does not furnish the actual energy for the vital activities of the protoplasm. This is furnished principally by the dextrose derived from the proteid. Although it is necessary to abandon the older theory which pronounces glycogen (or dextrose) a direct cleavage product of proteid, still the explanation of Rubner remains tenable if interpreted in the newer light. If the energy requirement of the cell remains constant at 100, even after the ingestion of 140 calories of proteid, then 71.4 per cent. of the total heat value of the proteid is the quantity actually used for the vital processes. Since it has been shown in the writer's laboratory that meat proteid yields 58 per cent. of dextrose in metabolism, it may be calculated that 52.5 per cent. of the total energy of proteid may be available for the cells in the form of sugar. A balance of 19 per cent. must be obtained from other compounds, while 28.5 per cent. of the total heat value is wasted as heat without ever having been brought into the service of the life processes of the cells. Perhaps this 28.5 per cent. of heat loss represents the quantity produced by the cleavage of proteid into amino bodies and the denitrogenization of these radicles.

The constancy of the energy requirement in metabolism makes difficult the explanation of the action of the various ferments found in the body. These are of two varieties, hydrolytic and oxidizing, but these from the very principles of our knowledge must be subservient to the requirement of the living cells, and not themselves masters of the situation, as, for example, they are in the autolysis of dead tissue. It seems to be the requirement of the mechanism of cell activity which determines metabolism, and not primarily the action of enzymes, whose influence appears to be only intermediary.

Friedenthal[26] shows that proteid, colloidal carbohydrates, fats and soaps are not oxidizable in the cellular fluids without previous hydrolytic cleavage. After hydrolysis, however, the oxidases may effect an oxidation of the smaller molecules. The necessity of the hydrolytic ferment is seen in the non-combustion of dextrose after the extirpation of the pancreas, the organ by which the ferment is supplied. Oxygen and the oxidases are present in ample quantity, but the sugar is not burned unless it be broken by its specific ferment. In the meantime the cell avails itself of a compensatory energy supply from other sources. It is impossible to apply anything similar to Ehrlich's side-chain theory to this condition of affairs, for the metabolism does not depend upon the satisfaction of chemical affinities, but rather upon a definite law of utilization of energy equivalents.

However clearly formulated the laws of metabolism may be, and many of them are as fixed and definite as are any laws of physics and chemistry, still the primary cause of metabolism remains a hidden secret of the living bioplasm.

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[25] Rubner, 'Gesetze des Energieverbrauchs,' 1902, p. 380.

[26] Friedenthal, 'Verhandlungen der Berliner Physiologischen Gesellschaft,' *Archiv für Physiologie*, 1904, p. 371.

SCIENTIFIC BOOKS.

Notes on Anthropoid Apes. By the Hon. Walter Rothschild.

This paper, in the last number of the *Proceedings of the Zoological Society of London*